UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,302	03/07/2001	Patrick F. Kelly	2427/1G685US1	2679

29311 7590 02/13/2002

DARBY & DARBY
805 THIRD AVENUE
NEW YORK, NY 10022-7513

EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)	
Office Action Summary	09/801,302	KELLY ET AL.	
	Examiner	**Art Unit**	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *19-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Notice of References Cited	Application/Control No. 09/801,302	Applicant(s)/Patent Under Reexamination KELLY ET AL.	
	Examiner Celine Qian	Art Unit 1636	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Moritz et al., Fibronectin improves transduction of reconstituting hematopoietic stem cells by retroviral vectors: Eveidence of direct viral binding to chymotryptic carboxy-terminal fragments, 1996, BLOOD, Vol. 88, pp. 855-862
	V	Uchida et al., HIV, but not murine leukemia virus, vectors mediate high efficiency gene transfer into freshly isolated G0/G1 human hematopoietic stem cells, 1998, PROC. NATL. ACAD. SCI. USA, Vol. 95, pp. 11939-11944
	W	Porter et al., Comparison of efficiency of infection of human gene therapy target cells via four different retroviral receptors, 1996, HUMAN GENE THERAPY, Vol. 7, pp. 913-919
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

DETAILED ACTION

Claims 1-37 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 8 is acknowledged. The traversal is on the ground(s) that some of the Groups belong to same class and subclass, therefore the search will be co-extensive. The applicants further argue that the claims of Group I contain unifying features with the claims of Groups II-VI and the search of Group I will overlap with the search of Groups II-VI. The applicants explain that (at page 5 of the Response) co-culturing stem cells with producer cells is another way of contacting vectors with the target cells. This is found partially persuasive because the applicants have established the evidence that the stem cells in claims 17 and 18 cannot be produced by other methods. However, the stem cells in claims 19 and 20 read on a subset of transduced stem cells that are engrafted into a host, these cells cannot be produced by the method of Group I without additional method steps. The claims in Groups III-VI are patentably distinct for the reasons of record as set forth in the prior office action mailed on 12/5/2001. Although the Groups may have same classification, however, the search is not co-extensive because the search would require different emphasis. Therefore, it would be a burden to search all the groups.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-18 are currently under examination on merits. Claims 19-37 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "highly efficient" in claims 1-18 is a relative term which renders the claims indefinite. The term "highly efficient" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what percentage of cells should express the gene of interest thus the method of transducing stem cells would be considered as highly efficient. Therefore, the metes and bounds of the claims cannot be established.

The word "substantially" renders the claims indefinite because it is not clear to what extend the vector particles need to be free of factors, producer cells and producer cell supernatant. It is also unclear what percentage of cells need to be undifferentiated. As such, the metes and bounds of the claims cannot be established.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the gene of interest is expressed in transduced stem cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8, 12-14, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Porter et al (1996).

The claims are drawn to a method of transducing stem cells by contacting a retroviral vector particle containing a gene of interest and pseudotyped with feline endogenous virus RD114 envelope protein, wherein the stem cells are hematopoietic cells isolated from cord blood cells, mobilized peripheral blood cells, bone marrow or liver. Claims 17 and 18 are drawn to a population of stem cells transduced with vector particles pseudotyped with RD114 envelope protein.

Porter et al. disclose the relative efficiency of transduction of bone marrow cells by retroviruses bearing the envelopes of amphotropic murine leukemia virus (MLV-A), xenotropic murine leukemia virus (MLV-X), gibbon ape leukemia virus (GALV), feline leukemia virus subgroup V (FeLV-B), and feline endogenous virus RD114 (see abstract). Porter et al. also disclose that infection of bone marrow cells with a retroviral (oncoviral) vector comprising a lacZ gene and vector bearing MLV-A, GALV and RD114 envelope proteins is efficient as measured by lacZ expression in the transduced cells (see material and methods, *Generation of helper-positive and helper-free MFGnlacZ pseudotypes,* and page 917, table 3 and 4). Porter et al. further disclose the CD34+ cells isolated from bone marrow are infected with similar

efficiencies by packaging with all those envelope proteins (see page 915, 2nd column, lines 1-3). Porter et al. also disclose a population of stem cells transduced with vector particles pseudotyped with RD114 (see table 3). Therefore, Porter et al. disclose the instant claimed inventions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8, 10-14, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Porter et al. as applied to claims 1, 2, 8, 12-14, 17 and 18 above, and in further view of Moritz et al (1996).

The claims are drawn to a method of transducing stem cells with a retroviral vector particle pseudotyped with RD114 envelope protein and containing a gene of interest, wherein the retroviral vector particles are pre-adsorbed onto a surface coated with an adherence-promoting

agent, such as retronectin. The claims are further drawn to said method wherein the stem cells are prestimulated.

Porter et al. teach that RD114 pseudotyped virus for is efficient (at least as well as MLV-A and GALV, see table 3 on page 917) in gene delivery to stem cells. Porter et al. also teach that viruses bearing RD114 envelope produced from certain human cells are stable in fresh human serum and offer the greatest potential for in vivo gene therapy (see abstract and page 917, 2nd column, last paragraph). However, Porter et al. do not teach the retroviral vector particles are pre-adsorbed onto a surface coated with an adherence-promoting agent. In addition, Porter et al. do not teach that using lentiviral vector for transduction, and pre-stimulating hematopoietic stem cells with cytokines.

Moritz et al. teach that fibronectin improves transduction of reconstituting hematopoietic stem cells by retroviral vector (see title). Moritz et al. also teach that such improvement is due to direct binding of retroviral particles to carboxyl-terminal chymotryptic fibronectin fragment, FN30/35 (see abstract and page 855, 1st column, 3rd paragraph, page 860, 2nd column, 3rd paragraph, lines 3-12). Moritz et al. further teach that cells are pre-stimulated with IL6, rhSCF and polybrene for 48 hours prior to retroviral infection (see page 856, second column, last two lines).

It would have been obvious to one of ordinary skill of art to develop a method of transducing stem cells with a retroviral vector pseudotyped with RD114 envelope protein and having the viral particles pre-adsorbed onto a surface that promotes adherence of the retroviral vectors. The ordinary artisan would have been motivated to do so because of the combination of teaching of Porter et al. and Moritz et al., both teaching methods in improving transduction

efficiency of retroviral vectors to hematopoietic cells. Porter et al. teach that RD114 pseudotyped virus is efficient in gene delivery to stem cells with the added advantage of not being inactivated by human serum. Moritz et al. teach that adherence of viral particles to fibronectin fragment increases the transduction efficiency of retroviruses. It would have been obvious to one of ordinary skill of art to combine the teaching of Porter et al. and Moritz et al. and develop a method to improve retroviral transduction efficiency to stem cells. The ordinary artisan would have a reasonable expectation of success because of the teaching of Porter et al., who demonstrate that retroviral vector pseudotyped with RD114 envelop protein efficiently transduced CD34+ bone marrow cells, and the teaching of Moritz et al., who demonstrate that adherence of viral particles to fibronectin improves transduction efficiency of hematopoietic cells. It would also have been obvious to one of ordinary skill in the art to develop a method to improve transduction efficiency of hematopoietic stem cells using retroviral vector pseudotyped with RD114 envelope, and pre-stimulate cells with cytokines. The ordinary artisan would have been motivated to do so because of the combined teaching of Porter et al., who teach RD114 pseudotyped virus is effective in transducing CD34+ bone marrow cells, and Moritz et al., who teach a method of pre-stimulation of cells with cytokines prior to retroviral transduction. The ordinary artisan would have reasonable expectation of success because of the teaching of Porter et al., who teach RD114 pseudotyped virus is effective in transducing CD34+ bone marrow cells Moritz et al., who demonstrate the method for transducing hematopoietic cells using fibronectin and cytokine pre-stimulation result in effective cell transducntion. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-3, 7, 8, 9-14, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Porter et al. as applied to claims 1, 2, 8, 12-14, 17 and 18, and in further view of Uchida et al (1998).

The claims are drawn to a method of transducing stem cells with a retroviral vector pseudotyped with RD114 envelope protein and containing a gene of interest, wherein the retroviral vector is a lentiviral vector, and the vector particles are freed of producer cells and supernatant by ultracentrifugation. The claims are further drawn to said method wherein the stem cells are hematopoietic cells from either cord blood cells, mobilized peripheral blood cells, bone marrow cells and liver, said stem cells are CD34+ or CD34+/CD38-. The claims are further drawn to said method wherein the stem cells are pre-stimulated with cytokines, growth factors and phytohemagglutinin.

Uchida et al. teach lentiviral vector (HIV-1 based vector) mediate high efficiency gene transfer into highly purified hematopoietic stem cells (see abstract, and page 11944, 1st column, 2nd paragraph, lines 1-2, and page11941, figure 2C &E). Uchida et al. also teach that the viral stocks used for transduction were concentrated, thus removing producer cells and supernatants by ultracentrifugation (see page 11940, 2nd column, lines 11-14). Uchida et al. also teach that the purified hematopoietic stem cells (either CD34+/CD38- or CD34+/CD38+) can be stimulated with thrombopoietin, FLK2L and SLF for 3 days prior to transduction (see page 11940, 2 column, 2nd paragraph). Uchida et al. also teach that pre-stimulation with cytokines would stimulate hematopoietic stem cells into cell cycle before transduction (see page 11943, lines 9-10).

It would have been obvious to one of ordinary skill in the art to develop a method to improve transduction efficiency of hematopoietic stem cells using lentiviral vector pseudotyped with RD114 envelope, and pre-stimulate cells with cytokines. The ordinary artisan would have been motivated to do so because of the teaching of both Porter et al. and Uchida et al. Porter et al. teach that retroviral vector pseudotyped RD114 envelope protein is efficient in gene delivery to stem cells with the added advantage of not being inactivated by human serum. Uchida et al. teach that using lentiviral vector in transducing hematopoietic cells isolated from mobilized peripheral blood is efficient. In addition, Uchida et al. teach pre-stimulation the cells with cytokines stimulate cells into cell cycle. The ordinary artisan would have a reasonable expectation of success because Porter et al. demonstrate efficient gene transfer by viral vector psuedotyped with RD114 envelope protein, and Uchida et al. demonstrate that lentiviral vector improves transduction efficiency of hematopoietic stem cells over MLV vector. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 15 and 16 are free of art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
February 10, 2002

REMY YUCEL, PH.D
PRIMARY EXAMINER